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PATENT
Customer No. 60,949
Attorney Docket No. 1142.0378-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
James H. PICKAR et al.	)	Group Art Unit: 1617
	)	
Application No.: 09/808,878	)	Examiner: Shengjun WANG
	)	
Filed: March 15, 2001	)	
	)	
For: HORMONE REPLACEMENT THERAPY	)	Confirmation No.: 5270
	)	

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY BRIEF UNDER RULE § 41.41

Pursuant to 37 C.F.R. § 41.41, Appellants present this Reply to the Examiner's Answer dated February 24, 2006. If any fees are required in connection with the filing of this paper, Appellants request that the required fees be charged to Deposit Account No. 06-0916.

I. Status of Rejection

In response to the Appeal Brief filed November 14, 2005 the Office has maintained the rejection of claims 7, 11, 12, and 69 under 35 U.S.C. § 103(a) as being unpatentable over Plunkett et al. (U.S. Patent No. 4,826,831 (RE 36,247)) ("Plunkett").

II. Response to Office's Arguments

Appellants maintain their position that, for the reasons of record and for the additional reasons set forth below, a *prima facie* case of obviousness has not been established, and even if it has been established, Appellants have demonstrated that the claimed invention achieves unexpected and surprising results.

A. The Examiner's Answer Fails to Provide Motivation for Optimizing Teachings of Plunkett et al.

In the Answer, the Examiner asserts:

> One of ordinary skill in the art would have been motivated to employ conjugated equine estrogen/medroxyprogesterone in the specific dosages claimed herein in a method of treating hot flashes because they (dosages herein) fall within the therapeutic ranges of the conjugated equine estrogen/medroxyprogesterone taught by the prior art [Plunkett et al.]. Optimization of amounts is within the purview of the Skilled Artisan, and is therefore obvious absent evidence to the contrary. No such evidence is seen.

Examiner's Answer at 4. In making this statement, the Office fails to explain what **in the prior art** would suggest or motivate a person of ordinary skill in the art to optimize the teachings of Plunkett et al. when the reference already discloses "preferred" dosages for a series of estrogens and progestins. More specifically, the Office has not explained why a person of ordinary skill in the art would ignore the explicitly preferred dosages listed of 0.600 mg/day for conjugated equine estrogens (CEE) (col. 4, line 65) and of 2.5 mg/day for medroxyprogesterone acetate (MPA)(col. 5, line 50) in order to arrive at the claimed dosages of about 0.45 mg/day to about 0.3 mg/day for CEE and 1.5 mg/day for MPA. The case law requires such as explanation: "Even when obviousness is

based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab,* 217 F.3d 1365, 1370 (Fed. Cir. 2000).

B. The Examiner's Answer Fails to Address Explicit Disclosure in the Art That Teaches Away From Appellants' Claimed Invention

Moreover, the Office has not addressed the fact that both the Plunkett et al. reference applied in the rejection, as well as the contemporary literature cited in the Lobo Declarations, actually teach away from Appellants' claimed dosages. The range reported in Plunkett et al. Table 1A for conjugated equine estrogens is 0.300 to 2.5 mg/day, with a preferred dose of 0.600 mg/day. Col. 4, line 65. The reported range for medroxyprogesterone acetate is 1 to 15 mg/day with a preferred dose of 2.5 mg/day. Col. 5, line 50. One cannot seriously dispute that, in designating the preferred amounts, Plunkett et al. taught that those particular amounts *were* the optimal amounts. After all, "preferred" means chosen "as more desirable or more valuable." American Heritage College Dictionary, p. 1078, 3rd ed., 1997.

The Office's rejection, however, assumes that a person of ordinary skill reading the Plunkett et al. disclosure of the preferred and optimal dosages of estrogens and progestins would somehow be motivated to find some *other* optimal amounts, even though the optimal amounts were already disclosed. Indeed, the disclosed preferred amounts taught away from the claimed dosages. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02 (emphasis in original) (citing *W.L. Gore &*

Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)). Here, there is no need for anyone skilled in the art to seek to find the optimal dosages within the disclosed ranges since, while reading Plunkett et al., a person of ordinary skill in the art would recognize the "preferred" dosages as the optimal ones. That disclosure of "preferred" dosages of 0.600 mg of CEE and 2.5 mg of MPA would teach away from "optimizing" the dosages to arrive at a dosage regimen of about 0.3 to about 0.45 mg of CEE and about 1.5 mg of MPA, as recited in Appellants' claimed methods.

Other evidence of record confirms that the preferred dosages recited in Plunkett et al. were actually considered to be the **minimally effective** dosages for treating hot flushes by those of ordinary skill in the art, and thus would have taught away from Appellants' claimed dosage scheme. For example, the Second Declaration of Rogerio A. Lobo, M.D. states:

> For the past 20 years, the dosage of 0.625 mg CEE [conjugated equine estrogen] has been accepted as the **minimum dosage** of estrogen necessary to relieve the symptoms of menopase, including hot flushes and bone loss. (See, e.g., Sobel NB, Obstetrics and Gynecology Clinics of North America, 21: 299-319 (1994) (describing 0.625 mg as the standard dose of conjugated estrogen) (Ex. A hereto); Kronenberg F., Chapter 9: Hot Flashes, in Rogerio A. Lobo, ed., Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, New York, NY: Raven Press, at 109 (1994)) ("The most commonly used regimen for treating hot flashes in the United States in 0.625 to 1.25 mg of oral conjugated equine estrogen (Premarin)")(Ex. B hereto). The dosage of 2.5 mg of MPA [medroxyprogesterone acetate] has been recognized as the **minimum amount needed** to oppose 0.625 mg CEE and protect the endometrium. This combination of 0.625 mg CEE plus 2.5 mg MPA daily has been the most commonly prescribed combination estrogen-progestin hormone replacement therapy in the United States. (See, e.g.,

> Kreling, D., et al., Prescription Drug Trends: A Chartbook Update, Menlo Park, CA: Kaiser Family Foundation, at 51 (2000))) (Ex. C hereto).

Pages 1-2, ¶ 2 (emphasis added); *see also* First Lobo Declaration, pages 3-4, ¶ 8. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness that must be considered. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986); MPEP § 2145. Here, Appellants have provided objective evidence that the claimed invention represents a complete break from accepted wisdom in the art concerning the minimally acceptable dosage scheme for treating hot flushes with combination estrogen/progetin hormone replacement therapy. That accepted wisdom, along with the teaching of preferred dosages in Plunkett et al., teaches away from Appellants' claimed methods. Accordingly, the Office has failed to establish a *prima facie* case of obviousness of Appellants' claimed methods.

C. The Examiner's Answer Fails Appreciate the Evidence of Unexpected Results

In addressing Appellants' data, which sets forth the results of a double blind clinical study of postmenopausal women using various combinations of PREMARIN® plus MPA, or placebo (*see* Specification, pages 8-11), the Office asserts:

> [T]he data presented does not constitute unexpected results because according to appellants' remarks, the data shows similar efficacy of the following regimens: 0.625 CEE/2.5 MPA, 0.45 CEE/1.5 MPA, 0.30 CEE/1.5 MPA. Some data points are overlapping in both number and severity of hot flushes.

Examiner's Answer at 5. Apparently, the Office's position is that because there is a *similarity* in results for the three dosage schemes, there is no showing of unexpected

results. However, the similarity in results is achieved by using lesser amounts of the active ingredients and was, therefore, surprising. Indeed, the similar results obtained with differing amounts of active ingredients evidenced that the claimed dosage scheme possessed an "unexpected superiority in potency which itself is conclusive of nonobviousness." *See In re Lunsford,* 357 F.2d 380, 380, 148 USPQ 716 (CCPA 1966).

Moreover, there is no requirement that, for unexpected results to be shown, there must be an *increase* in relative activity between the data point representing the closest prior art (here, 0.625 CEE/2.5 MPA) and the claimed invention (here, 0.45 CEE/1.5 MPA, 0.30 CEE/1.5 MPA). *See In re Chupp,* 816 F.2d 643, 646, 2 USPQ2d 1437 (Fed. Cir. 1987) ("To be patentable, a compound need not excel over prior art compounds in all common properties.") Where a person of ordinary skill in the art would have expected any difference in results, a showing of similarity is evidence of unexpected results that must be considered. *See In re Orfeo,* 440 F.2d 439, 441, 169 USPQ 487 (CCPA 1971) ("As long as there is a question of obviousness, no matter how trivial that question may seem, we think appellants have the right to have considered the Rule 132 affidavit which allegedly shows new and unexpected results.") While a change in activity can be evidence of unexpected results, the "absence of [a] property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness" as well. *See* MPEP 716.02(a) (citing *Ex Part Mead Johnson & Co.,* 227 USPQ 78 (Bd. Pat. App. & Interf. 1985)).

Here, the claimed invention is a method of treating or inhibiting vasomotor symptoms, such as hot flushes. The method comprises orally providing a daily dosage of a combination of between about 0.45 mg and about 0.3 mg per day of CEE and about 1.5 mg of MPA. Plunkett et al. describes estrogen/progestin combination therapy for treatment of numerous disorders. Numerous estrogens and progestins are described as being useful, but the Office relies on Plunkett et al.'s recitation in Table 1A of a dosage of CEE from 0.300 to 2.5 mg/day, with a preferred dose of 0.600 mg/day, and a dosage of MPA of from 1 to 15 mg/day with a preferred dose of 2.5 mg/day. Those preferred dosages have been confirmed as the minimally effective dosages for treating hot flushes in the Lobo Declarations and the supporting literature mentioned above.[1] Thus, a person of ordinary skill in the art reading this disclosure of Plunkett et al. would have expected a *decrease* in the art-recognized minimal dosage to result in a *decrease* in activity, *i.e.,* would have expected a dose-dependant response. In fact, Dr. Lobo has stated with respect to the testing described in Appellants' specification:

> I and others expected that the study would show that there would be a dose response such that the lower combination doses of CEE and MPA would have some effect in reducing the number and severity of hot flushes compared with the placebo, but far less of an effect than the standard dose of CEE 0.625 plus 2.5 mg MPA.

First Lobo Declaration, pages 4-5, ¶12.

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1 Dr. Lobo has explained hat "[f]or purposes of treating or inhibiting vasomotor symptoms, one skilled in the art would consider a daily dosage of 0.600 mg CEE to be clinically equivalent to a dosage of 0.625 mg CEE." Second Lobo Declaration, page 2, ¶ 3.

The results set forth in the specification, however, have been interpreted by a person of ordinary skill in the art as "very surprising and unexpected" in that they show, not a dose-dependant *decrease* in activity, but a *similarity* in activity. *See* First Lobo Declaration, page 5, ¶14. The fact that there was *no decrease* in activity when a person of ordinary skill in the art would have expected a dose dependant response represents the "absence of [a] property which [the] claimed invention would have been expected to possess based on the teachings of the prior art." *See id.; see also In re Waymouth,* 499 F.2d 1273, 1276, 182 USPQ 290 (CCPA 1974) (reversing Board's obviousness rejection in view of unexpected results showing difference in kind, rather than degree, of claimed critical range even where results showed operability over ranges outside claimed range). Additionally, the fact that Appellants have demonstrated an unexpected increase in potency for the claimed dosage scheme "is conclusive of nonobviousness." *See In re Lunsford,* 357 F.2d 380, 380, 148 USPQ 716 (CCPA 1966). Thus, the fact that the claimed method results in a similarity, rather than a decrease, in activity is truly surprising and unexpected and is sufficient to overcome the rejection of the pending claims over Plunkett et al.

III. Conclusion

Accordingly, Appellants respectfully request that the rejection be reversed and withdrawn and that claims 7, 11, 12, and 69 be allowed.

Please grant any extensions of time required to enter this reply brief and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

Dated: May 23, 2006

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